Effect of Selecting a Fixed Dephosphorylation Rate on the Estimation of Rate Constants and rCMRGlu from Dynamic [^{18}F] Fluorodeoxyglucose/PET Data

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Several publications have discussed the estimation and physiologic significance of regional [^{18}F]fluorodeoxyglucose (FDG) rate constants and metabolic rates. Most of these studies analyzed dynamic data collected over 45–60 min; three rate constants (k_1-k_3) and blood volume (V_b) were estimated and the regional cerebral metabolic rate for glucose (rCMRGlu) was subsequently derived using the measured blood glucose value and a regionally invariant value of the lumped constant (LC). The dephosphorylation rate constant (k_4) was either neglected, or a fixed value was used in the estimation procedure to obtain the remaining parameters. To compare the rate constants obtained by different authors using different values of k_4 is impossible without knowledge of the effect of selecting different fixed values of k_4 (including zero) on the estimated rate constants and rCMRGlu. Based on our analysis of FDG/PET data from nine normal volunteer subjects, we conclude that inclusion of a fixed value for k_4, in spite of a scaling effect on the absolute values of model parameters, has no effect on the coefficient of variation (CV) of within- and between-subject parameter estimates and glucose metabolic rates.

J Nucl Med 30:1483–1488, 1989

Phelps et al. (*1*) extended the original model of Sokoloff et al. (*2*) to include the dephosphorylation of FDG-6-PO_4, which proceeded slowly in normal subjects, but was nonetheless significant, depending on how long after injection rCMRGlu was measured. Since then, several attempts have been made to incorporate the dephosphorylation rate constant, k_4, into both the dynamic and single-scan techniques. Previous authors have emphasized the futility of fitting k_4 as an additional parameter for studies of less than 1 hr duration (*3–6*). Most recently, Evans et al. (*7*) suggested that the preferred method of dealing with the issue of dephosphorylation was to include k_4 in the operational equation, with a fixed value equal to a population average obtained from long duration studies. Huang et al. (*8*) demonstrated that neglecting k_4, i.e., setting k_4 to zero, underestimates the true metabolic rate and that this estimation error increases linearly with postinjection scan time.

At present, there is no information in the literature about the intra- and intersubject variability in FDG model parameters as a function of selecting fixed values of k_4 for scans acquired 45–55 min after radiopharmaceutical injection. This is a standard nonlinear estimation problem in which the constraints on one parameter create biased estimates in the unconstrained parameters. We, therefore, studied the effect of selecting different fixed values of k_4 on the parameter estimates derived from dynamic and single-scan techniques for data collected 45–55 min after the injection of FDG.

METHODS

Experimental Protocol

FDG/PET studies were performed on nine normal volunteer subjects (aged 27 ± 3 yr) as described by Rottenberg

Received Dec. 22, 1988; revision accepted Apr. 20, 1989.

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et al. (*9*). All subjects were fasted overnight and allowed a light breakfast 6 hr before FDG/PET scanning. FDG, produced by a modification of Tewson's synthesis (*10,11*), was more than 97% radiochemically pure (specific activity 500 mCi/mmol). Serial PET images (10 × 1 min, 5 × 2 min, 3 × 5 min, 3 × 10 min) were obtained with the PC 4600 positron camera (*12*) following the injection of 5–10 mCi of the tracer during a controlled resting state with the patient's eyes patched and auditory stimulation (music and intermittent verbal briefings) delivered through acoustically isolated earphones. The time course of plasma ^{18}F radioactivity was determined by sampling radial arterial blood at frequent intervals and counting aliquots of plasma in a scintillation well detector. Brain and blood radioactivity curves were aligned using measured arrival times (*13*).

Data Analysis

Region of interest (ROI) analysis was performed on 128 × 128 PET reconstructions which were corrected for random coincidences and electronic deadtime. Tissue attenuation was accounted for by using a transmission scan. Correction was applied to compensate for the global scaling effects of scatter in transmission, cross-calibration, and emission scans (*14*). Twenty-four (12 per hemisphere) standardized cortical and subcortical gray matter (GM) ROIs, two cerebellar and two brainstem ROIs were outlined on reconstructed PET brain slices with reference to co-planar CT scans and/or a neuroanatomic atlas (*15*). Because many of these anatomic ROIs were outlined on multiple planes, the total number of ROIs for a given subject was usually 49. Compartmental GM rate constants (k_1–k_3) and cerebral blood volume (V_b) were estimated from the time course of blood and regional brain radioactivity at three different fixed values of k_4 (0, 0.0068, 0.0136) (*7,9*). Glucose utilization for the dynamic study, $(rCMRGlu)_D$, was calculated as $(Cp/LC)*(k_1k_3)/(k_2+k_3)$. Individual subjects' mean rate constants, averaged across GM ROIs, were used to "functionalize" images, i.e., convert raw-count images into images with glucose metabolic rate units, mg/100g/min, acquired between 45 and 55 min after tracer injection as described by Sokoloff et al. (*2*) and Phelps et al. (*1*). The k_4 value was fixed at the same value used in the optimization process for the determination of k_1–k_3. rCMRGlu values were derived by averaging the upper 10% of functionalized ROI pixel values; rCMRGlu values obtained in this way were termed "autoradiographic" and designated $(rCMRGlu)_A$. Whenever anatomic regions straddled contiguous PET brain slices, rCMRGlu was calculated by weighting component ROI values by the number of thresholded pixels. The lumped constant (LC) was assumed to be 0.42. The within-subject CVs in parameter estimates were obtained by first calculating the CV over 24 cortical and subcortical ROIs for each subject, followed by averaging these CVs over all subjects. All rCMRGlu data was entered into a SAS (SAS Institute Inc., Cary, NC) database for statistical analysis.

Statistics

Linear regression was performed for two cases: (a) on mean parameter estimates for different subjects and (b) on regional parameter estimates within a subject. For the between-subject case, mean of each parameter over GM ROIs was calculated for every subject and linear regression analysis was carried out on (1) mean $\hat{k}_1$ (at $k_4 = 0.0068$) versus mean $\hat{k}_1$ (at $k_4 = 0.0$), and (2) $\hat{k}_1$ (at $k_4 = 0.0068$) versus $\hat{k}_1$ (at $k_4 = 0.0136$). This regression procedure was repeated for all four parameter estimates as well as calculated estimates of subject mean metabolic rates. For the second case (within subject), similar linear regression analysis was performed except that there were 49 data points corresponding to 49 ROIs within a given subject.

RESULTS

Table 1 contains the results from the parameter estimation procedure for nine normal subjects when k_4 was fixed at 0.0068. Estimated values of k_1, k_2, k_3, cerebral blood volume (V_b) and rCMRGlu, and their coefficients of variation, are summarized in Tables 1 and 2. CVs of all GM rate constants are, in general, lower by ~5% when thalamus and basal ganglia are excluded (results not tabulated, but quoted here to provide comparison with the results of several authors who exclude deep gray matter structures when reporting CVs in GM rate constants). The insensitivity of mean $(rCMRGlu)_A$ across GM regions, MR_A, to variations in the rate constants is reflected in the lower CV of MR_A compared to the corresponding mean $(rCMRGlu)_D$, MR_D (Table 2). Because of the high correlation between all parameters and the selection of only three values of k_4, it was deemed not useful to perform multivariate analysis of variance on the CVs, especially when no trend in CVs with k_4 was obvious (Table 2). The goodness of fit to the model, as judged by the least chi-square criteria, was similar at different selected values of k_4.

The high values for V_b (0.0865) in Table 1 are due to the smearing of the blood curves. Correcting these blood curves for smearing due to the external blood sampling system (*16*) resulted in a 32% decrease in V_b (bottom two rows in Table 1); all other parameters increased in value, the largest change being in k_2, which increased by 65%, and the smallest change in MR_A and MR_D, both of which increased by 3%. k_1 and k_3 increased by ~20%.

Figure 1A illustrates the results of the regression for each parameter estimate at different fixed values of k_4 (each data point corresponds to the mean parameter value for one subject); Figure 1B illustrates similar regressions for MR_A and MR_D. In these scatter plots, regression lines were constrained to pass through the origin. The rate constants k_1, k_2, and k_3 are plotted over the same ranges to show the small variation in k_1 when compared to that of k_2 and k_3. The results of statistical testing to determine where data points in each scatter plot fall along the line of identity are reported in Table 3 (all statistical testing was done on regression lines that were *not* constrained to pass through the origin; see Discussion).

The effects of different fixed values of k_4 on estimated parameters over 49 ROIs within a single subject were

TABLE 1
Parameter Estimates for $k_4 = 0.0068$

Subject	Age (yr)	k_1	k_2	k_3	V_b	MR_D	MR_A
1	30	0.0767	0.1119	0.1049	0.0641	9.78	9.21
		±0.0097	±0.0413	±0.0335	±0.0140	±1.54	±0.88
2	26	0.0769	0.0583	0.0446	0.1181	7.55	7.42
		±0.0075	±0.0222	±0.0212	±0.0198	±1.56	±0.90
3	29	0.0878	0.1061	0.0960	0.1005	11.25	9.14
		±0.0163	±0.0631	±0.0365	±0.0214	±1.41	±1.23
4	29	0.0790	0.0647	0.0649	0.0987	9.55	7.79
		±0.0106	±0.0348	±0.0271	±0.0161	±1.25	±1.03
5	30	0.0761	0.0864	0.0983	0.1069	10.08	8.80
		±0.0140	±0.0553	±0.0440	±0.0216	±1.54	±0.58
6	24	0.0616	0.0647	0.0939	0.1115	9.77	8.49
		±0.0091	±0.0392	±0.0436	±0.0202	±1.28	±0.84
7	22	0.0638	0.1075	0.1009	0.0615	7.87	7.05
		±0.0076	±0.0509	±0.0406	±0.0116	±1.20	±0.80
8	27	0.0727	0.1027	0.0748	0.0654	8.81	8.22
		±0.0077	±0.0408	±0.0189	±0.0144	±0.87	±0.74
9	23	0.0894	0.1441	0.1576	0.0522	11.36	10.01
		±0.0143	±0.0750	±0.0506	±0.0141	±0.93	±1.22
Mean	27	0.0760	0.0940	0.0929	0.0865	9.56*	8.46*
s.d.	±3	±0.0088	±0.0264	±0.0296	±0.0239	±1.24	±0.89
Mean†	27	0.0902	0.1548	0.1147	0.0584	9.89	8.75
s.d.†	±3	±0.0108	±0.0492	±0.0288	±0.0252	±1.10	±0.84

* $MR_D > MR_A$. Possible reasons include (1) lack of blood volume correction in the operational equation and (2) different scan times; MR_A based on 45-55 min scan and MR_D based on 0–40 min kinetic data.

† Data reanalyzed with smear-corrected blood curves (*16*).

Abbreviations: All values are given as mean ± s.d. k_1-k_3, FDG rate constants (l/min); V_b, cerebral blood volume (ml/g); MR, mean rCMRGlu across gray matter regions (mg/100g/min). Subscripts A and D refer to "autoradiographic" and "dynamic" calculations, respectively.

similar to the scaling effects illustrated in Figure 1 and the regression results in Table 3.

DISCUSSION

Selection of k_4

Various values of k_4 (determined in normal volunteer subjects) are available in the literature: 0.0068 ± 0.0014 (mean ± s.d., n = 13, study duration 3 hr) (*1*), 0.0055 ± 0.0009 (n = 9, study duration up to 5 hr) (*17*). Hawkins et al., (*18*) found k_4 to be 0.0075 ± 0.0031 (n = 8, study duration 3 hr) for normal gray matter in patients with brain tumors. Additionally, Friedland et al. (*19*) obtained a value of 0.0097 ± 0.0029 (n = 5, study duration 45 min) and Lammertsma et al. (*20*) found k_4 to be 0.015 ± 0.006 (n = 3, study duration 55 min) in normal subjects. A relatively short period of data collection (45 and 55 min) may have been responsible for the higher values of k_4 reported by the last two authors. The long half-time of k_4 precludes its accurate determination from the 45-min FDG/PET studies that are routine in many PET centers; Carson et al. (*3*) suggested that for $k_4 = 0.0068$, a study lasting at least 150 min was required for its accurate estimation. Thus, treating k_4 as a variable to be estimated by a nonlinear curve-fitting procedure is probably not justified when the study duration is <2 hr. Therefore, excluding the

TABLE 2
Coefficient of Variation (CV, %) in Parameter Estimates

	Within subjects					
	k_1	k_2	k_3	V_b	MR_D	MR_A
$k_4 = 0.0$	13.8	52.0	39.3	19.9	14.5	11.4
0.0068	14.0	50.2	38.7	20.3	13.8	10.8
0.0136	15.7	54.8	42.1	21.0	14.4	10.8
	Between subjects					
$k_4 = 0.0$	10.8	24.5	29.0	27.1	13.5	11.1
0.0068	11.6	28.1	31.9	27.6	13.0	10.5
0.0136	11.6	29.1	30.2	28.4	12.8	10.1

Abbreviations: k_1-k_3, FDG rate constants; V_b, cerebral blood volume; mean rCMRGlu across gray matter regions. Subscripts A and D refer to "autoradiographic" and "dynamic" calculations, respectively.

last two studies results in a mean value of k_4 for normal gray matter to be 0.0066.

The results of regression analysis (Fig. 1B and Table 3) suggest that changing k_4 results in a change in the mean metabolic rates. The mean metabolic rates change in their absolute values by the amount predicted by previous error analysis (a 1% error in k_4 resulted in a 0.05–0.1% error in rCMRGlu for a scan duration of 40–50 min (*8*); in our data a 100% change in k_4 (from 0.0068 to 0.0136) resulted in an increase of ~5% in MR_A and MR_D. For $k_4 = 0$, however, the decrease in MR_A was larger (~15%) than the decrease in MR_D (~5%); this is consistent with the fact that the change in rate constants is observed to be symmetrical with respect to the change in k_4 around a mean value of 0.0068 (Fig. 1), resulting in a symmetrical change in MR_D. MR_A is calculated from the operational equation, which is nonlinear with respect to k_4; the result is a smaller change in MR_A when k_4 increases from 0.0068 to 0.0136 than when k_4 increases from 0.0 to 0.0068. The operational equation tends to underestimate MR_A by ~10% for a scan duration of 40 min when k_4 is neglected (*6,8*). At the same time, the near linearity in the scatter plots (Fig. 1, Table 3) suggests that the relative values of the calculated metabolic rates, between and within subjects, are not markedly altered by assuming an arbitrary but fixed value of k_4.

The regression lines in Figure 1A indicate that in-

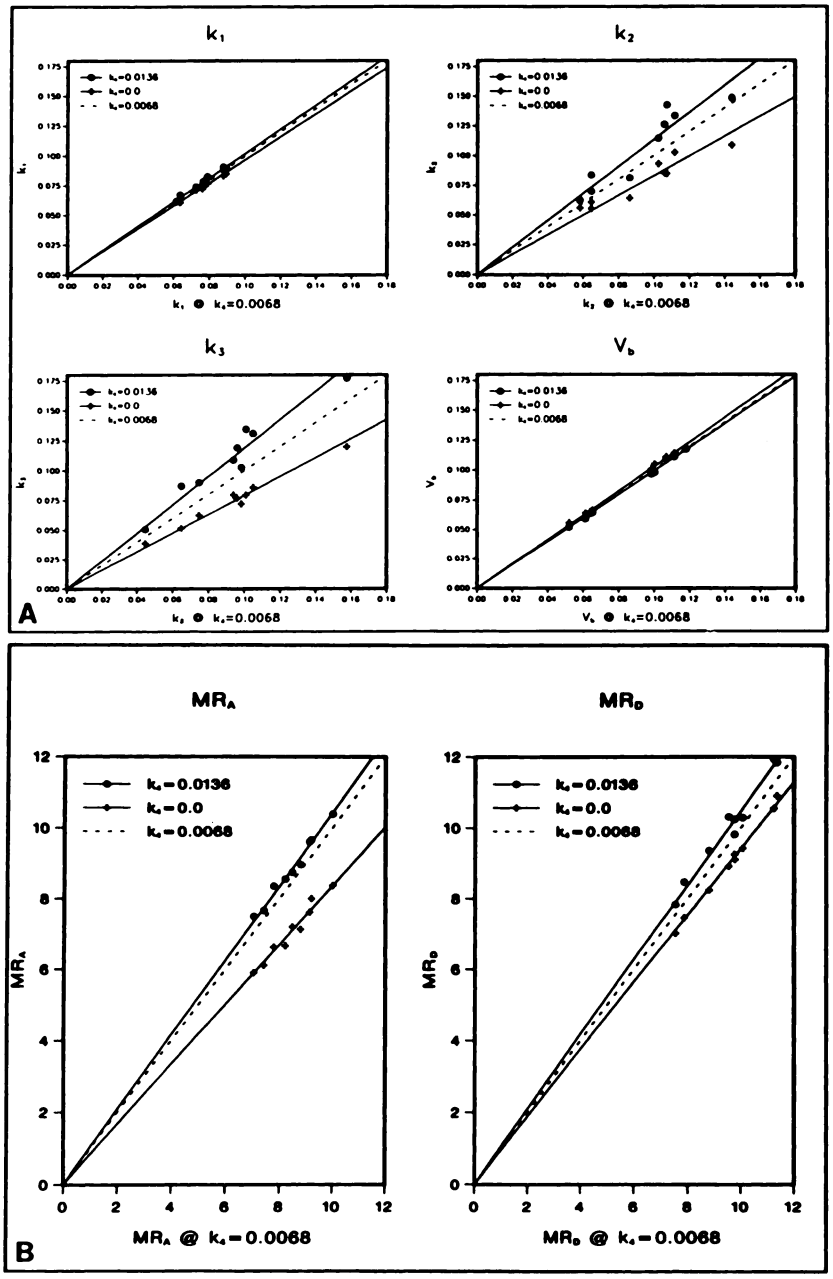

FIGURE 1
Effect of changing k_4 on the mean parameter values for nine subjects. A: Estimates of k_1, k_2, k_3, and V_b. k_4 was fixed at one of the three selected values and the abovementioned parameters estimated using kinetic data. The abscissa corresponds to the parameter estimate when k_4 = 0.0068. The two solid lines are regression lines through the nine subject data points when k_4 = 0.0 and k_4 = 0.0136 with zero intercept constraint (see text). The dotted line represents the line-of-identity, which corresponds to the ordinate being the parameter estimate when k_4 = 0.0068. B: Calculated mean metabolic rate for "autoradiographic" (MR_A) and "dynamic" (MR_D) calculations.

TABLE 3
Results of Linear Regression Analysis for Nine Patient Studies*

Parameter estimates at $k_4 = 0.0068$	k_4: Fixed values	
	0.0	0.0136
Fitted parameters		
k_1	0.90, 0.0055† (0.98)	1.00, 0.0013¶ (0.97)
k_2	0.69, 0.014† (1.90)	1.10, 0.0038§ (0.87)
k_3	0.72, 0.0071† (0.98)	1.10, 0.0091‡ (0.94)
V_b	1.01, 0.0017‡ (1.00)	1.02, −0.0023¶ (1.00)
Calculated metabolic rates		
MR_A	0.86, −0.024† (0.96)	1.00, 0.39† (0.98)
MR_D	0.97, −0.31† (0.99)	1.02, 0.29‡ (0.97)

Estimated parameter values for $k_4 = 0.0068$ were regressed against corresponding parameter values obtained for $k_4 = 0.0136$ and $k_4 = 0.0$. All values are given as slopes, intercept (R^2: squared correlation coefficient or fractional variance accounted for).

† $p < 0.001$ (test the null hypothesis that the regression line is the line-of-identity, slope = 1, intercept = 0).

‡ $p < 0.01$.

§ $p < 0.05$.

¶ $p > 0.05$.

Abbrevations: k_1-k_3, FDG rate constants; V_b, cerebral blood volume; mean rCMRGlu across gray matter regions. Subscripts A and D refer to "autoradiographic" and "dynamic" calculations, respectively.

creasing the assumed value of k_4 increases the estimates of the rate constants k_1, k_2 and k_3—least for k_1, while decreasing slightly the value of V_b. In other words, ignoring the regional and/or subject variation in normal k_4 will have its largest effect on k_2 and k_3. As in the case of metabolic rates, linearity is maintained, and the effect of k_4 on the estimated model parameters is also a scaling effect. Therefore, even if the primary interest of a study is the analysis of the rate constants themselves, the absolute value of k_4 selected during the model-fitting procedure will not distort between-subject comparisons.

The effect of k_4 on estimated as well as calculated parameters within a subject (49 ROIs) is similar to that observed between subjects. The results of regression analysis suggested that there were no statistical differences in the two cases of regressions—with and without the intercept constrained to zero. Therefore, Figure 1 was illustrated with the intercept fixed to zero in order to quantify the magnitude of the scaling effect for different fixed values of k_4.

This linear scaling effect on parameter values of a fixed k_4 demonstrates the preservation of within- and between-subject patterns (rank ordering of parameter values) when absolute values have an unknown systematic bias due to the unknown true value of k_4. The lack of effect of k_4 on parameter CVs (Table 2) is consistent with the fact that there is very little information about k_4 in the first 45 min of the study. If k_4 varied substantially from subject to subject, this variability should have been reflected in increased scatter in the data—resulting from different scaling effects for different subjects. The large R^2 values for the regression lines in Table 3 argue against such variability; long duration studies have already shown a small intersubject variation in the estimate of k_4 (20% COV) (*1*).

In the case of certain diseases, when k_4 changes significantly, it is not possible to pinpoint the underlying physiologic cause based on the absolute value of the parameters (especially k_2 and k_3) because of the variable scaling effect of different k_4s. However, relative ordering of parameters, which holds true for a fixed value of k_4, can be used to provide a first order physiologic state discrimination. Techniques that overcome the scaling effects have already been developed and can be very effective in FDG/PET data analysis (*21,22*).

The scaling effects on various parameters discussed above are applicable to nonsmear corrected blood data. Our partial smear correction compensates only for external smearing (radial catheter and pump tubing) and we do not yet have a quantitative description of individually varying internal smearing (circulatory system) required to confirm the scaling effects on fully smear corrected data. This individual internal smearing could be similar in magnitude to the fixed external smearing (*16*). It is, however, expected that scaling effects on parameters for fully smear corrected data will be similar, albeit of a different magnitude, to those for the nonsmear corrected data for the following reasons: (a) the similarity of the CVs in the estimate of parameters for both partial smear and nonsmear corrected data sets (Table 1), (b) the similar percent magnitude change in parameter values for partial smear corrected data when k_4 was changed from 0.0068 to 0.0 and 0.0136 (tested for two subjects, 7 and 8, Table 1) and (c) smearing correction has a trivial effect on rCMRGlu determinations based on the autoradiographic technique. This

occurs because rCMRGlu values are governed primarily by the area under the blood curve, which is almost identical for smear and nonsmear corrected data.

CONCLUSION

At the present time, for FDG/PET studies of less than 1 hr's duration, the necessity for fitting k_4 as an additional parameter has not been demonstrated, although it would seem reasonable to include a fixed "population" value in the range 0.0055 to 0.0075 min^{-1} for gray matter, based on long-duration studies, in the operational equation. Inclusion of a fixed k_4 value has a scaling effect on all model parameters, but has no effect on the coefficient of variation of within- or between-subject values for homogeneous groups. This observation emphasizes the need for testing subject and/or group differences using pattern analysis techniques instead of absolute rCMRGlu values.

ACKNOWLEDGMENT

The authors thank Andrew Barclay and Filolaos Kefalas for help in data gathering and Maria Sergi for assistance with the data analysis. The credit for preparing this manuscript goes to George Abramson. This work was supported in part by grants NS-23473 and NS-03346 from the National Institute of Neurological and Communicative Diseases and Stroke.

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